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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/948,124	10/09/1997	ELLIS REINHERZ	DFCI-522A	6658

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	32

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/948,124	Applicant(s) REINHERZ ET AL.	
	Examiner Christopher H Yaen	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,45 and 63-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,45 and 63-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 22 & 27
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The examiner of the application has changed. This case has now been transferred as of 6/26/02. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

2. Amendments to the claims are acknowledged and amendments to claims 41, 45, 63 have been entered. Claims 41, 45, 63-71 are pending and considered on the merits

3. The petition to correct inventorship (paper no.19) is acknowledged.

Continued Examination Under 37 CFR 1.114

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/17/02 has been entered.

Information Disclosure Statement

5. The information disclosure statement filed on December 22, 2001 (paper no. 22) has been considered and a signed copy accompanies this action.

New Claim Rejections - 35 USC § 112

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 41,45,and 63-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. In regard to claims 41, 45, 63, and dependent claims thereof in the recitation of the phrase *"expressed in immature thymocytes as a result of T cell receptor stimulation with a peptide"*, it is unclear as to whether the activity of caspase/procaspase or the expression of the caspase/procaspase is mediated by the T cell receptor stimulation with a peptide. Clarification is required.

9. Claims 41, 45, 63-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors

to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claimed invention is drawn to a method of identifying an agent which and a method of enhancing the activity of a caspase/ procaspase expressed in immature thymocytes as a result of T cell receptor (TCR) stimulation with peptide, or an active derivative or fragment thereof.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that certain and specific molecules, compounds, and agents are able to activate ICE through binding to the TCR. On such example is the activation of ICE by TCR binding to glucocorticoid (Ohoka Y Int Immunol 1996 Mar; 8(3):297-306). However, the art does not teach variants or derivatives of peptides that are able to stimulate the TCR.

The amount of direction or guidance present and the presence or absence of working examples: The specification does not teach how to make and use variants or derivatives of peptides that can be used to stimulate or activate caspase/procaspase activity. The working examples are drawn to the inhibition of caspases following the stimulation of TCR by a peptide or a molecule that specifically activates

caspase/procaspase. None of the working examples found in the specification disclose or teach variants or derivatives that can be used to stimulate TCR.

The breadth of the claims and the quantity of experimentation needed: Given the broad range of the peptide fragments and derivatives encompassed within the claims, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

10. Claims 41, 45, 63-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only describes specific peptide which are capable of stimulating a TCR, and is not commensurate in scope with claims that read on derivative or fragments.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception the peptide(s) used in the instant specification, the skilled artisan cannot envision the detailed structure of the encompassed derivatives and or fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a

genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for derivatives or fragments is provided in the specification on page 4 lines 31. However, no disclosure, beyond the mere mention of derivatives or fragments of peptides is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an the peptide described in the instant specification that are capable of stimulating a TCR having an amino acid sequence meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 41 and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fearnhead *et al* (1995).

The claims are drawn to a method of identifying an agent which enhances the activity of a caspase/procaspase expressed in immature thymocytes as a result of TCR stimulation with a peptide (wherein the caspase activity is considered to be its ability to function as a protease and also is associated with apoptosis) and a method of enhancing a capase or procaspase expressed in immature thymocytes by an agent that is identified.

Fearnhead *et al* teach that ICE-like proteases (also known as caspase) are involved in thymocytes apoptosis (see Abstract; and pages 285-286), as well as methods to detect the activity of the ICE-like proteases (also known as caspases) by using agents that can inhibit their activity.

Fearnhead *et al* do not teach methods to enhance the levels or activity of caspase or procaspases in the thymocytes or isolated and purified caspases expressed in immature thymocytes. However, it was well known at the time of the invention that apoptosis occurred in thymocyte and played a vital role in thymic selection processes (Fearnhead *et al*). It was also known that ICE-like proteases were involved in these

events in the thymocytes (Fearnhead *et al*). Thus it would have been *prima facie* to one of ordinary skill in the art at the time of the claimed invention to substitute in the cell lysate employed by Fearnhead *et al* other agents that might have the property of enhancing the apoptosis by enhancing the ICE-like proteases (or caspase), since one of ordinary skill in the art would not expect the thymocyte cell lysates not to contain caspases. One of ordinary skill in the art would not have expected that caspases from these sources to be different if isolated and identified as a caspase-i.e the caspase of the claims were inherently present in the thymocyte lysate of Fearnhead *et al*, and were expressed in the thymocyte. The assays taught by Fearnhead *et al* inherently measured the activity of caspases. One of ordinary skill in the art would have been motivated to use the same thymocyte lysate system since thymocytes are involved n immune regulation, in self-recognition events and implicated in mechanisms of clonal deletion by apopotic pathways. The teachings of Fearnhead *et al* provides the motivation as well as a reasonable expectation of success that studies of apoptosis in thymocytes could be done using the methods in Fearnhead *et al* which teaches assays to identify agents that can modulate apoptosis and apply the same methods to identify agents that enhance activities of the caspases expressed in the thymocyte lysate.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
June 29, 2002

Brenda Brumback
BRENDA BRUMBACK
~~PATENT~~ EXAMINER
PRIMARY